Remarks/Arguments

Claims 50-52, 54, 56-75, 77, 79-95, 97-104 and 108-131 are pending. Claims 1-49, 53, 55, 76, 78, 96 and 105-107 remain canceled. No claims have been amended. No new matter has been added.

Rejections under 35 U.S.C. § 103(a)

Claims 50-52, 54, 56-75, 77, 79-95, 97-104 and 108-131 remain rejected as unpatentable over WO 98/07414 ("the '414 publication") in view of US Patent No. 5,976,577 ("Green") or US Patent No. 6,475,510 ("Venkatesh"). Applicants traverse.

The '414 publication names two inventors, Indu Parikh and Ulagaraj Selvaraj. Parikh is also a named inventor of the present application. Applicants previously submitted two declarations under 37 CFR § 1.132 by Indu Parikh (on September 28, 2009 and December 29, 2008, "the First Declaration" and "Second Declaration", respectively) to establish that Parikh invented the subject matter disclosed in the '414 publication and relied on in the rejection. Accordingly, Applicants argued that the '414 publication is not available as prior art to sustain a rejection under Section 103(a) in the pending application.

The First Declaration described the subject matter in the '414 publication invented by Indu Parikh as including

> "a process of preparing rapidly dispersing oral dosage forms of hydrophobic compounds wherein the particles are coated with at least two surfactants; wherein one of the surfactants was a phospholipid (surface modifying agent). The average particle sizes of the hydrophobic compound were less than 10 microns. The composition contained other materials such as cellulose and mannitol. The process of preparation involved mixing of the components (water insoluble active agent and the surface modifying agents) in an aqueous medium, sonicating it and lyophilizing the composition to form particles. The lyophilized powders could be converted into granules or tablets with the addition of binders and other excipients."

First Declaration at para. 5. To clarify, the '414 publication does not describe "rapidly dispersing oral dosage forms." Applicants believe this is undisputed, since the Examiner relies on Green and Venkatesh for their descriptions of a process for preparing a rapidly disintegrating

dosage form. See Office action at p. 3, first three paragraphs. And there is no such description in pages 2-8 of the '414 publication relied upon by the Examiner.

The Second Declaration described the contributions of co-author Ulagaraj Selvaraj as including "selecting a surfactant(s) that provide volume-weighted mean particle size values of the water-insoluble compound at least 50% smaller than particles produced without the presence of the surfactant using the same energy input." Second Declaration at para. 5.

The Examiner contends that the description in the Second Declaration of the contributions of Selvaraj implies that Selvaraj was "involved in the process of preparation" and that therefore the reference "still qualifies as an applicable reference." The Examiner apparently contends that the Declaration indicates Selvaraj's contribution to step (b) of claim 50. See the Office action at p. 4.

Assuming, *arguendo*, that Selvaraj contributed to step (b) of the claimed method, this does not render the entire '414 publication available as prior art against the present application. Instead, those portions of the '414 publication that were invented by Parikh, as established by the First Declaration, are not available as prior art against the subject application. Accordingly, the '414 publication is not available as prior art with respect to its description of *e.g.*, a process of preparing submicron size particles of hydrophobic compounds wherein the particles are coated with at least two surfactants, one of which is a phospholipid.

The '414 publication, absent the portions that describe the subject matter invented by Parikh, cannot sustain a rejection under Section 103(a), alone or in combination with Green and Venkatesh. This is because, absent the contributions of Parikh in the '414 publication, the combination of references fails to describe or suggest each and every limitation of the claimed methods. For example, the combination of references does not describe a step of *preparing an aqueous suspension of a water insoluble or poorly water-soluble drug in the presence of one or more surface stabilizing agents, of which at least one is a phospholipid*, which is required in step (a) of each of independent claims 50, 73, 97, and 98. For this reason alone, the '414 publication, in combination with Green and Venkatesh, fails to support a *prima facie* case of obviousness with respect to the claimed methods.

Further, Applicants submit that neither Green nor Venkatesh, nor their combination, describes how to make a rapidly disintegrating solid dosage form of a water insoluble or poorly

water-soluble active according to the claims. The process described by Venkatesh begins with a dry granulation mixture. See Venkatesh at col. 4, lines 10-37. Thus, Venkatesh does not describe a process that includes a step of admixing *a homogenous aqueous suspension* of a water insoluble active and a phospholipid with at least two rapidly dispersible matrix-forming agents as required by Applicants' claims. Nor does Venkatesh describe a step of drying the admixture to produce a solid having surface stabilized drug particles dispersed and embedded throughout a support matrix, wherein the support matrix dissolves or substantially disperses in a rapid disintegration time of *less than 2 minutes* upon contact between the solid and aqueous environment, as required *e.g.*, by step (d) of claims 50, 97, and 98, and step (c) of claim 73.

Green describes a method comprising the formation of a suspension in a continuous phase of *coarse particles* of active in a carrier. See Green at col. 2, lines 58-67. Coarse particles means particles greater than 100 microns. Green at col. 3, lines 1-22. Thus, Green does not describe a step of subjecting an aqueous suspension of a water insoluble drug and a phospholipid to a particle fragmentation process to form a homogeneous aqueous suspension of micron and submicron particles, *wherein the mean volume weighted particle size of the water-insoluble or poorly water-soluble drug particles in the suspension ranges between about 0.05 and about 10 micrometers*, as required by step (b) of claims 50 and 98, step (a) of claim 73, and step (c) of claim 97. Nor does Green suggest a method comprising a step of forming particles of active within the claimed size range. Instead, Green explains that coarse particles of drug are used because the available coating techniques were only able to effectively coat particles greater than 100 microns in size. Green at col. 3, lines 9-11. Green further explains that smaller particles may not have an intact coat, which "will result in rapid release of the drug once in suspension." Green at col. 3, lines 12-14. Green further explains that a coating agent is used to prevent loss of drug during processing and to delay its release beyond the point of disintegration of the dosage form in the mouth. Green at col. 3, lines 1-6. Thus, the skilled person following Green would not expect success in making a rapidly disintegrating solid dosage form of a water insoluble or poorly water-soluble drug according to the claims, which require formation of a homogenous aqueous suspension of micron and submicron sized particles.

At most, Green describes the use of phospholipid as a coating agent. Green at col. 5, lines 31-47. Green does not describe or suggest the use of phospholipid as a stabilizer for micron and

submicron sized particles of poorly soluble active, which are formed according to the claimed methods, *e.g.*, in step (b) of claim 50. Green does not describe or suggest a method which includes a step of preparing an aqueous suspension including primary particles of a water insoluble or poorly water-soluble drug in the presence of one or more surface stabilizing agents, *of which at least one is a phospholipid, wherein the concentration of the phospholipid in the aqueous suspension ranges from about 0.1% w/w to about 90% w/w*, as required by step (a) of claims 50, 73, 97, and 98; or (2)

In summary, the combination of references cited by the Examiner, absent the contributions of Parikh to the '414 publication, which are removed from consideration as prior art against the subject application by the First Declaration, does not describe each and every element of the claimed methods. Nor does the combination provide a reasonable expectation of success in making a rapidly disintegrating solid dosage form of a water insoluble active according to the claims.

Double Patenting Rejections

Claims 50-52, 54, 56-75, 77, 79-95, 97-104 and 108-131 remain rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-11 of U.S. Patent No. 5,922,355 ("the '355 patent") in combination with either Green or Venkatesh. Applicants traverse.

The claims of the '355 patent are directed to a process of preparing microparticles of compounds that are poorly soluble in aqueous media by mixing the particles with a phospholipid and at least one surfactant. The claims of the '355 patent do not encompass a method of making a rapidly disintegrating solid dosage form of a water insoluble or poorly water soluble drug and a phospholipid, as required by the pending claims of the subject application.

The Examiner contends that the preparation of a rapidly disintegrating solid dosage form is obvious in view of Green or Venkatesh. However, neither Green nor Venkatesh describes or suggests a method for making a rapidly disintegrating solid dosage form of a poorly soluble active according to the claims, as discussed above. Nor do the cited references provide a reasonable expectation of success in doing so, particularly in view of the art-recognized difficulties in formulating poorly soluble actives as well as the difficulties in formulating with

phospholipids. For example, phospholipids are "pasty" and hygroscopic, making them prone to agglomeration. To arrive at the present invention it was necessary to choose excipients which both minimize agglomeration and promote regeneration of the suspension of active particles when the dosage form contacts an aqueous medium. It was not predictable, prior to the disclosure of Applicants' invention, which combination of excipients would give rapid disintegration, *i.e.*, disintegration within less than 2 minutes, and regenerate a suspension of the active having no more than about 20% by weight of particle aggregation or agglomeration, as required by the pending claims. *See e.g.*, step (d) of claims 50, 97, and 98, and step (c) of claim 73. Accordingly, Applicants maintain that the pending claims are not *prima facie* obvious over the claims of the '355 patent in view of Green or Venkatesh and request that the rejection be reconsidered and withdrawn.

Claims 50-52, 54, 56-75, 77, 79-95, 97-104 and 108-131 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 2, 4-25, 45-47, 52, 53, 55, 56, 65 and 101-119 of co-pending application U.S. Serial No. 10/260,788 in combination with either Green or Venkatesh. Since the rejection is provisional, Applicants will address the rejection at such time as one or more of the claims in the present application or the conflicting application are deemed allowable.

Claims 50-52, 54, 56-75, 77, 79-95, 97-104 and 108-131 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 11-19, 23, 24, and 27-37 of co-pending application U.S. Serial No. 09/443,862 in combination with either Green or Venkatesh. Since the rejection is provisional, Applicants will address the rejection at such time as one or more of the claims in the present application or the conflicting application are deemed allowable.

Applicants submit that the application is in condition for allowance and request an action for same. Please charge any additional fees that may be due, or credit any overpayment, to Deposit Account No. 50-0311, Attorney Reference No. 28069-546001US.

Respectfully submitted,

/Muriel Liberto/

David E. Johnson, Reg. No. 41,874
Muriel Liberto, Reg. No. 55,382
Attorneys for Applicants
MINTZ, LEVIN
Tel: 617-542-6000
Fax: 617-542-2241
Customer No. 30623

Date: May 20, 2010

ACTIVE 4910091v.1